

A Novel Treatment of Patients with Chronic Hepatitis C

Naoky C.S. Tsai MD, Neil Shimoda MD, Linda Wong MD, Stanley Shimoda MD,
Kimberly Goad RN, Herbert Yee, Miles Chen

Abstract:

Objectives: Interferon alpha-2b therapy for Chronic Hepatitis C patients has been unsatisfactory. Recombinant Granulocyte Macrophage Colony-Stimulating Factor has been shown to have anti-viral effects in vivo and in vitro via cytokines release.^{1,2,3} Recently its effects on chronic hepatitis B and possibly chronic hepatitis C were reported.^{4,5} We, decided to conduct a pilot study to evaluate the anti-viral effects of recombinant human GM-CSF mono-therapy in patients with chronic hepatitis C and to assess its side effects.

Methods: A total of 10 patients (male/female: 5/5) (age: 34-60, mean: 45) seen in our center between 2/95 to 2/96 were randomly selected to receive recombinant human Granulocyte Macrophage Colony-Stimulating-Factor at 125 ug/m2 subcutaneously daily for two weeks followed by three times weekly for another 8 weeks. Biochemical (ALT) and viral (HCV-RNA) responses were measured prior to treatment and at weeks four and eight. Side effects were recorded.

Results: Six out of the ten patients treated had significant viral reduction but none became negative. Eight out the ten patients treated showed biochemical improvement and three out of the eight had normalized liver enzymes. Age, sex, stage of the disease did not influence the response but there seems to be a tendency for patients with higher pre-treatment viral level to respond virally. Side effects are minimal and well-tolerated.

Conclusion: Recombinant human Granulocyte Macrophage Colony-Stimulating-Factor in the dose used has anti-viral effects in the majority of the chronic hepatitis C patients studied. Side effects are minimal and well tolerated. Further study with higher doses and longer duration is needed to prove its clinical efficacy in treating patients with chronic hepatitis C.

Introduction:

In the past few years since interferon alpha 2-b (IFN) was licensed for treatment of some patients with chronic hepatitis C, it has become clear that standard IFN therapy (3 million units subcutaneously three times a week) produces a complete biochemical response in 50% of patients (normalization of ALT at the end of treatment); however, the majority of responders relapsed after termination of therapy. To improve these results, many therapies have been tried including retreatment with same dose or escalating

interferon dosage, iron depletion therapy, and prolonged interferon therapy, but the beneficial results have not yet been established.

Among the different groups of biological response modifiers, GM-CSF (Granulocyte Macrophage-Colony Stimulating Factor) is a hormone-like glycoprotein cytokine produced by activated T lymphocytes, endothelial cells and fibroblasts that stimulates the proliferation, maturation and function of hemopoietic cells, augments and modifies the immune system, and regulates the secretion of other cytokines which are involved in the immune response to viral hepatitis. Recently J. Martin. et al reported HBV-DNA level reduction with GM-CSF alone or in combination with interferon alfa-2b.² Furthermore, in vitro studies of cytokine production by PBMC(peripheral blood mononuclear cells) during GM-CSF treatment revealed enhanced spontaneous production of other cytokines.¹

In the treatment of chronic hepatitis C, recombinant GM-CSF has been used mainly to rescue leukopenic patients during treatment with interferon alpha 2-b. There has been no clinical study in the U.S. to investigate if recombinant GM-CSF by itself has any anti-viral effect against hepatitis C virus. Therefore we decided to conduct a pilot study treating chronic hepatitis C patients who failed previous interferon alfa 2-b therapy with recombinant GM-CSF alone to observe if there is any anti-HCV effect and to assess its side effects.

Patients and Methods:

Ten patients (five males) with a mean age of 45 yr. (Range 34-60) who were seen in a tertiary center between 2/95 to 2/96 were selected to participate in this trial. The patient's clinical characteristics can be seen in Table I. All patients had failed previous interferon therapy and were off interferon or other immunological therapy for at least six months and met the inclusion and exclusion criteria. The protocol was approved by the IRB of the institution. Consent forms were signed. After the initial screening visit, all participants received recombinant GM-CSF (manufactured by Immunex Co. Seattle, Washington) at 125 ug/m2 subcutaneously daily for two weeks followed by three times a week for another eight weeks. Biochemical (ALT) and viral response (b-DNA method from Chiron Inc. Summerville, California) were assessed prior to treatment and at week four and eight. Side effects were assessed in each follow-up visit and recorded.

Results:

Of the ten patients treated with GM-CSF, six had significant viral titer reduction during the first two weeks of daily subcutaneous injection. However, none had eradicated the virus. Eight out of the

Correspondence to:
Naoky C.S. Tsai MD,
The Liver Center
St. Francis Medical Center
2228 Liliha St., #306
Honolulu, HI 96817

Naoky C.S. Tsai MD
Associate Professor of Medicine
Chief, Section of Hepatobiliary Disease
Division of Gastroenterology
Department of Medicine
John Burns School of Medicine, University of Hawaii

Table 1.— Patient Characteristics

Patient	Sex	Age	Genotype	Histology	PreRx RNA (10 ³)
D.H.	M	57	1b	CAH	>570
E.J.	F	35	1a	CPH	326.9
F.T.	M	42	1a	CPH	68.6
F.R.	M	45	?	CAH	41.8
L.Y.	F	59	1b	Cirrhosis	167.5
K.G.	F	34	1a	CPH	188.1
M.L.	F	49	4a	Cirrhosis	Not Done
O.D.	M	35	3a	CPH	133.7
R.J.	M	39	2b	Cirrhosis	<3.5
S.L.	F	60	1b	CPH	46.9

CAH = Chronic Active Hepatitis

CPH = Chronic Persistent Hepatitis

ten treated showed ALT improvement and among them three had normalized ALT. The clinical data of all ten patients are shown in Table I. Three are genotype 1a, three type 1b, one type 2b and three untypable. Six patients had advanced liver disease and the remaining four had mild to moderate disease. Age, sex, stage of disease did not influence the response but there seems to be a tendency for patients with higher viral level to respond. Fig. I, Fig. IIa and IIb show mean HCV-RNA and ALT level of each patient respectively.

Side effects were minimal and well tolerated. The most common side effect was injection site irritation. Other side effects included flu-like symptoms (which were milder than that of interferon alpha 2-b) and general malaise. Two patients experience urticaria which responded to anti-histamine treatment. No cardiopulmonary side effects such as CHF or asthma attack were noted. Leukocytosis responses were universal and several patients had eosinophilia (up to 40% in one case with urticaria) but dose reduction was not needed.

Discussion:

Interferon therapy for chronic hepatitis C has been unsatisfactory in attaining sustained response in the majority of patients. Clearly enhancement of the response rate is needed. Of all the anti-viral therapies, interferons were the only agents shown to have anti-viral effect on hepatitis C virus. Ribavirin and Corticosteroids as monotherapy have been tested but without success in eradication of

Figure I.— HCV-RNA Level Changes During Treatment (x100,000 Copies/ml.) Patient's HCV-RNA level pre- and during GM-CSF therapy. No patient has eradicated HCV-RNA but there seems to be a downward trend in the level of HVC-RNA especially in the first four weeks of therapy when daily GM-CSF was administered. (Chiron version 1.0 Quantiplex method).

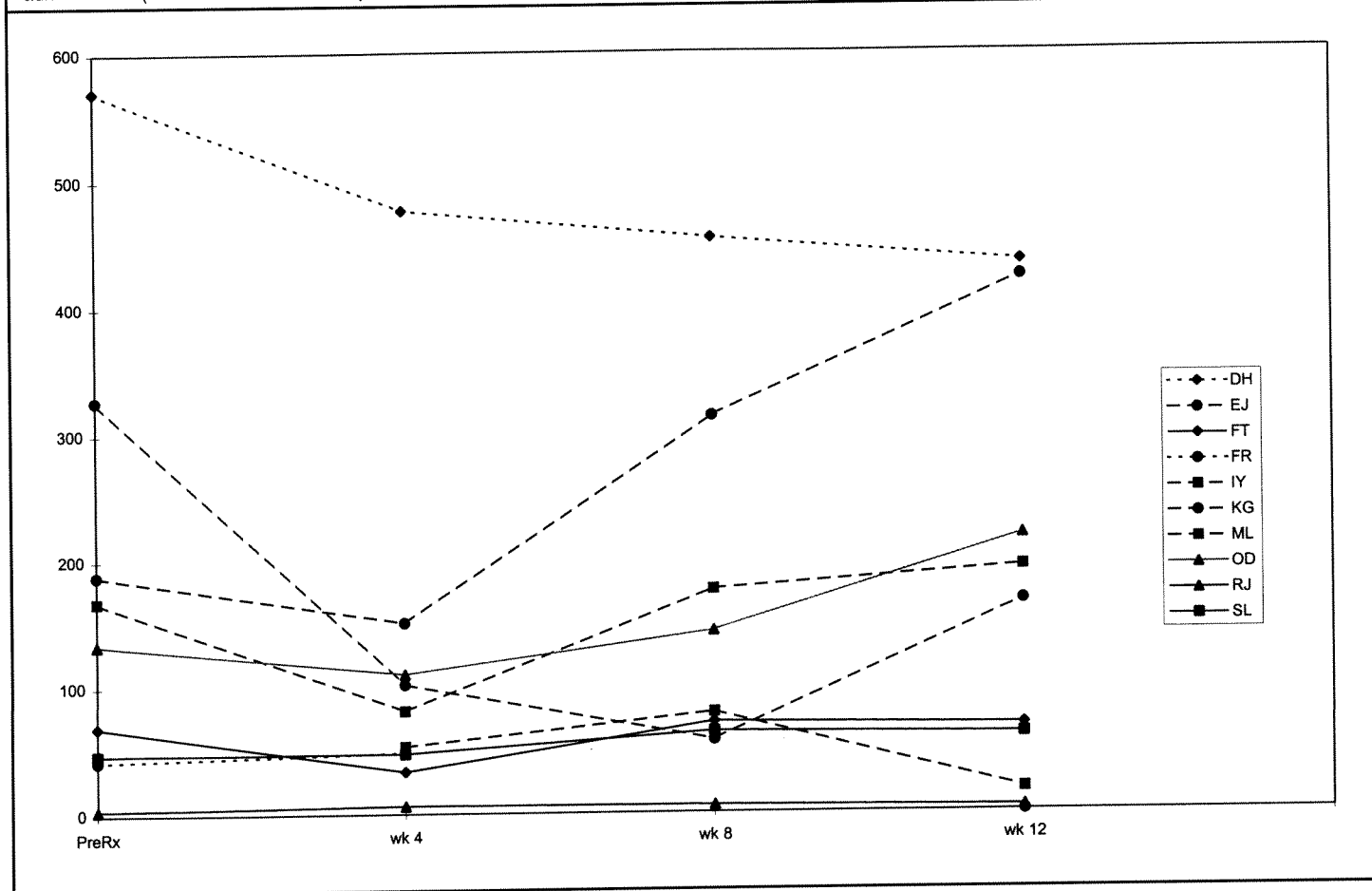


Figure IIa.— ALT Levels (I.U./ml) (ALT level of five patients during treatment.)

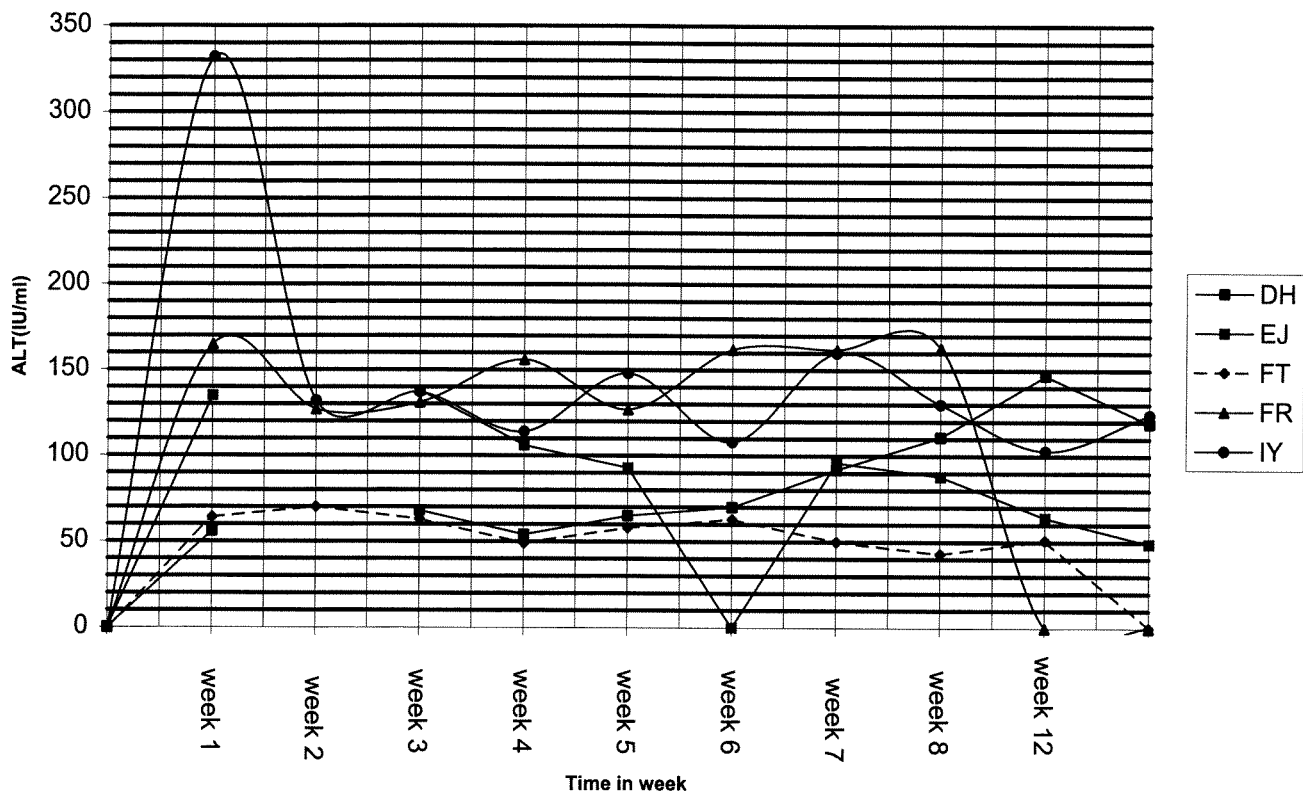
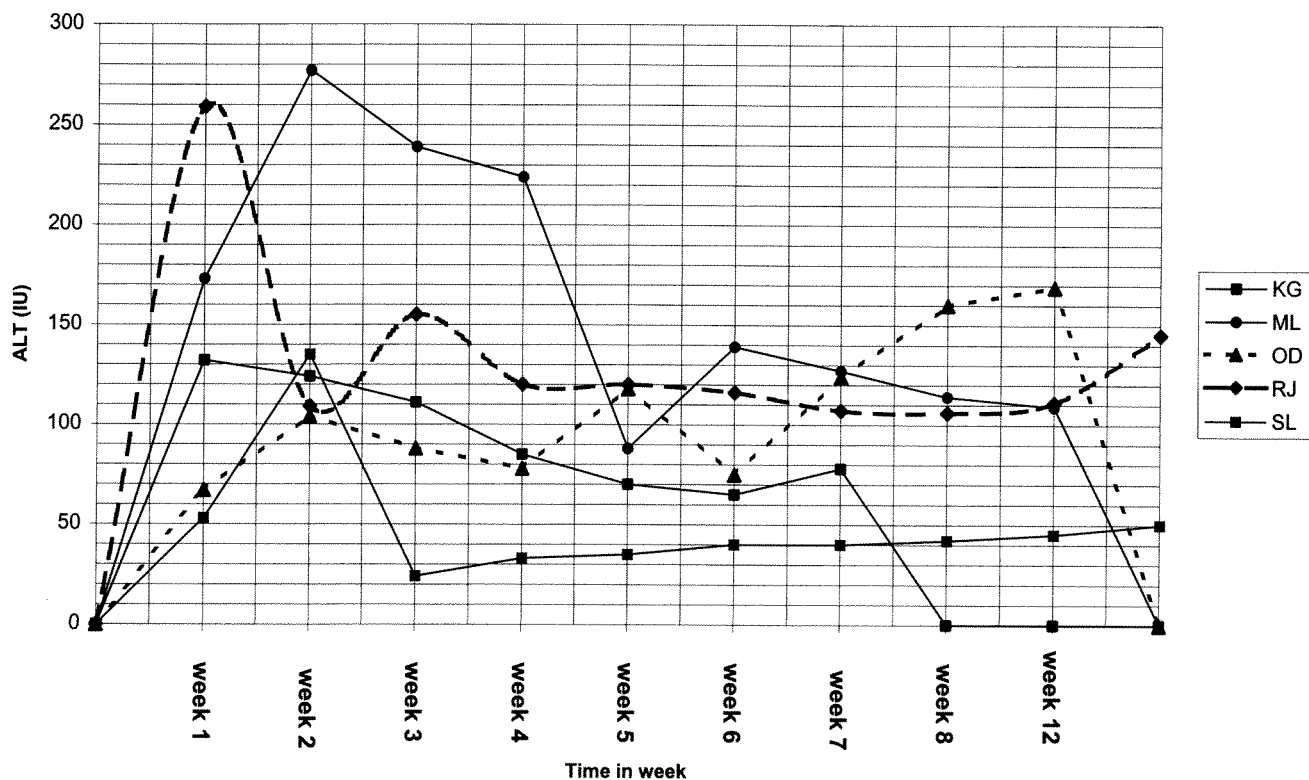


Figure IIb.— ALT Levels (I.U./ml) (ALT of another five patients during treatment.)



the virus. GM-CSF has been used to rescue patients with leukopenia on high dose interferon therapy⁴ but its efficacy as monotherapy for the treatment of chronic hepatitis C has not been tested. In this study we administered rhGM-CSF to ten patients who have failed previous interferon alpha 2-b treatment to study its anti-HCV effect and to assess side effects. The dosage given is low at 125 mcg/m² subcutaneously. The therapy was well tolerated with no significant side effects. No dose reduction was needed and no patient withdrew from the study. The leukocytosis occurred as expected and eosinophilia was observed in two patients. Local injection site irritation was common but generally manageable. Other side effects such as flu-like symptoms were much milder compared to that of the interferon therapy these patients had experienced previously, even during the daily rhGM-CSF administration in the first two weeks of the trial.

The reduction in the viral RNA during the treatment was significant in the majority of the patients especially during the daily dosing period. ALT was also noted to have improved in eight of the ten patients with normalization in three patients. These effects may be due to cytokine production by the GM-CSF effect. GM-CSF has been shown to increase the liberation of TNF-alpha (Tumor Necrosis Factor Alpha), Interleukin-2^{1,2,3} which themselves have potent antiviral activity.^{6,7,8}

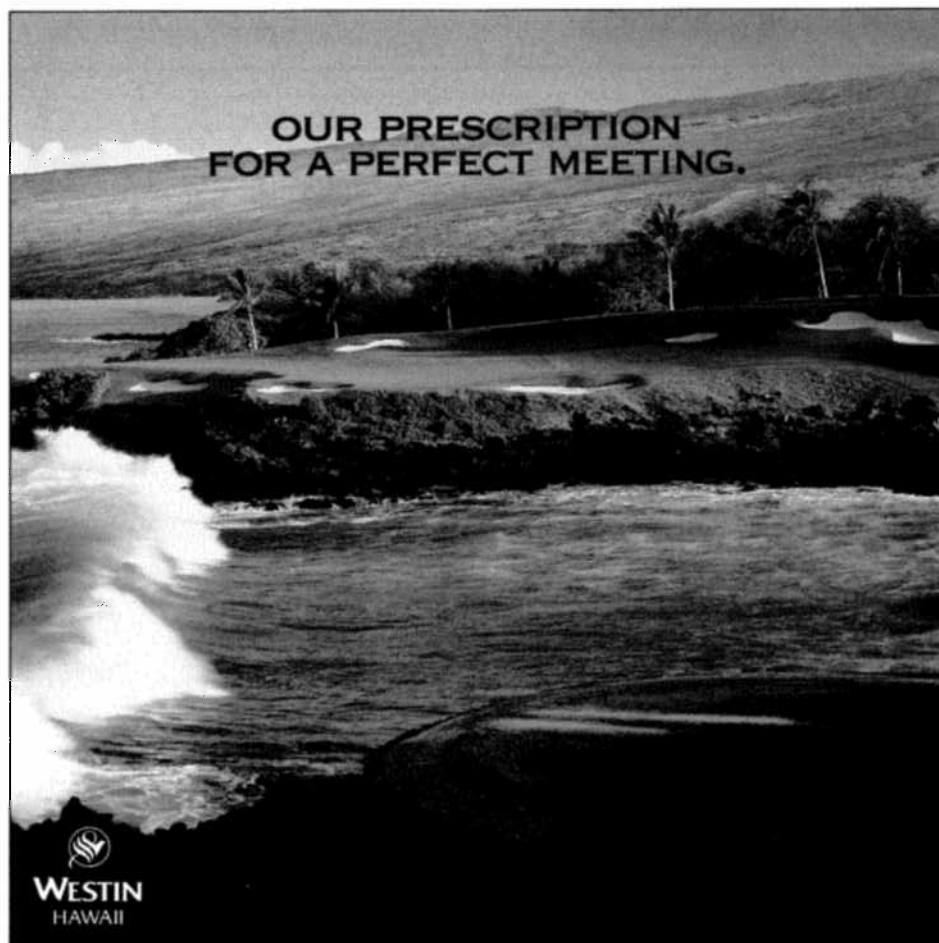
In summary, the administration of rhGM-CSF in the doses used is safe and well tolerated. The treatment seems to exert an anti-viral

effect on patients with chronic hepatitis C infection. Future studies with higher dosage and longer duration of therapy or in combination with interferon therapy are needed to prove its clinical efficacy as an alternative and/or adjuvant therapy for patients with chronic hepatitis C. GM-CSF could also play a role in the treatment of those patients with chronic hepatitis C who have significant leukopenia and were excluded from interferon therapy.

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